

Hypothesis: Possible immunological interference between POLYSORBATE 80 of the adjuvant flu vaccine and SARS-CoV-2 as a cause of the coronavirus pandemic

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AUTHOR'S NOTE

This work has been carried out on a strictly personal basis by the signatory, and Barbastro Hospital as an institution has no connection with him.

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OBJECTIVE

The groups most affected by COVID-19 in Spain have been and continue to be those over 65 years of age, people with chronic diseases, health professionals and members of the State Security Forces and Corps. The almost total coincidence with the groups targeted by the flu vaccination campaign was a suggestive sign of a possible correlation, and was the starting point for the study.

Subsequently, no published study was found in which the administration of the flu vaccine was considered a possible risk factor in relation to COVID-19, despite the fact that it is just another medicine and therefore susceptible to causing adverse reactions, and despite the fact that the 2019-2020 vaccination campaign was carried out in November and December 2019, i.e. just before the first cases of COVID-19 appeared.

During the state of alarm declared for the pandemic, several health professionals have carried out extra research activity to try to contribute to its resolution.

Part of the efforts have been directed at monitoring treatments for which there was a lack of evidence of efficacy against COVID-19, such as hydroxychloroquine. In the face of this approach, our efforts have been directed at trying to clarify the causes of the coronavirus pandemic first, and relegating the study of possible treatments to a later stage.

Research is and has been the priority objective of the study, and its publication has always been considered secondary. Despite this, the working documents have been written in a format that resembles a published article, to facilitate their monitoring by other health professionals from different fields to whom they have been sent, seeking their collaboration and criticism, which has been achieved in a significant way.

Once the alarm was raised, it was not possible to recruit a significant number of patients to allow for a rigorous statistical analysis, and the work remained editorially unfinished, making it difficult to publish under the established

rules. Nevertheless, the work could have its value, and the finding of relevant data could perhaps serve as a theoretical basis for future research, or reveal errors made. It is in this spirit that it is made public.

SUMMARY

Based on an epidemiological analysis of deaths from COVID-19 in the Health Sector attended by Barbastro Hospital, and the study of the pharmacotherapeutic history of the affected patients, it was found that the most common drug found in all the people who died was the adjuvant flu vaccine. This led to the hypothesis that flu vaccination with the adjuvant flu vaccine in the 2019-2020 campaign could be associated with a higher risk of death from COVID-19 in people over 65 years, i.e., a suspicion of possible iatrogeny, which was increased when data from another sector were accessed.

A possible mechanism of action for the hypothesis of immunological interference with parenteral POLYSORBATE 80 was proposed, and the degree of agreement of the expected data with the observed data was compared.

Keywords: COVID-19, adjuvant flu vaccine, POLYSORBATE 80, immune interference, cytokine storm

Hypothesis: Possible immune interference between POLYSORBATE 80 of the adjuvanted influenza vaccine and SARS-CoV-2 as a cause of coronavirus pandemic

ABSTRACT

Based on an epidemiological analysis of COVID-19 deaths in the Health Sector attended by the Hospital of Barbastro, and the study of the pharmacotherapeutic history of affected patients, it was found that the most common drug to all the deceased was the adjuvanted influenza vaccine. This led to the hypothesis that the influenza vaccination of the 2019-2020 campaign with the adjuvanted influenza vaccine could be associated with an increased risk of deaths by COVID-19 in people over 65 years of age, that is to say, to the suspicion of a possible iatrogenesis, suspicion that increased when accessing data from another sector.

A possible mechanism of action is proposed for the hypothesis of immunological interference with parenteral POLYSORBATE 80, and the degree of concordance of the expected data is compared to those observed, concluding that the hypothesis could be valid, and that is why it is decided to publish it.

Key words: COVID-19, adjuvanted influenza vaccine, POLYSORBATE 80, immunological interference, cytokine storm.

INTRODUCTION

Pharmacovigilance is part of the daily work of the hospital pharmacist, who must be vigilant in preventing and, where appropriate, detecting and resolving possible cases of adverse effects due to medicines in the patients he attends. To do this, he must often call upon other colleagues, both health and non-health professionals, all united in the common cause of the health of the population.

Influenza vaccination is a globally accepted health tool. Its effectiveness in preventing complications such as pneumonia, hospitalization and general mortality in institutionalized elderly people with comorbidities has been evaluated by studies with a high number of cases, although showing some not entirely consistent results (2).

Influenza vaccines are registered drugs that contain both inactivated virus components and excipients, are not free of the possibility of adverse effects, and should be monitored in the same way as other drugs received by patients in a study.

MATERIAL AND METHODS I

Confirmed cases of death by COVID-19 were recorded at the hospital itself on 30/04/2020, and all their previous treatments were analysed. Later, on 05/05/2020, the study was extended to the entire Health Sector, in order to enlarge the sample, using the Electronic Medical Record (EHR) as a data source.

RESULTS I

According to the User Database (BDU) consulted at the Primary Care Secretariat, the Health Sector served by Barbastro Hospital, which geographically occupies the eastern half of the province of Huesca, serves a total population of 111,490 inhabitants, of whom 24,561 are over 65 years of age: 22%.

The first relevant data found is the fact that the 20 deaths from COVID-19 in the Barbastro Sector were all over 65 years old: 100%.

According to the Weekly Epidemiological Bulletin of Aragon (1), the vaccination rate in the Barbastro Health Sector in the 2019-2020 campaign in this age group was 63.1%. In other words, 63 out of every 100 adults have been vaccinated, with the adjuvant vaccine corresponding to them.

The second relevant data obtained was that, of the 20 deaths due to COVID-19, 18 (90%) had the administration of the adjuvant vaccine recorded by Primary Care, and of the remaining 2, there was no record. In other words, 90 out of every 100 deaths from COVID-19 had been vaccinated with the adjuvant vaccine.

If the previous flu vaccination with the adjuvant vaccine did not interfere positively or negatively in the prognosis of those infected by COVID-19, it could be expected that both percentages were similar.

However, this is not the case. According to the results obtained, in the Barbastro Sector, patients who fall ill with COVID-19 and have the adjuvant flu vaccine die more than patients with COVID-19 who have not been vaccinated against the flu in the last campaign.

In other words, according to data from the Barbastro Sector, flu vaccination with the adjuvant vaccine would not only not have improved the prognosis of the elderly vaccinated with respect to COVID-19, but would have made it worse.

CONCLUSIONS I

The results obtained led us to hypothesize that flu vaccination in the 2019-2020 campaign with the adjuvant vaccine could be associated with a higher risk of death from COVID-19 in people over 65 years of age, which was

disseminated through both internal and external channels, highlighting the proposal made on the mailing list of the Spanish Society of Hospital Pharmacy (SEFH) to carry out the same study in other larger hospitals to expand the sample.

We received kindly collaborative responses from a few small hospitals, but it was impossible to combine their data with ours, since either they were not exclusively limited to the deceased or we did not have access to the detailed tracking of vaccination records that we perform in our EHR.

Here the work was completed, but when the conclusion was communicated, the low number of cases meant that they were immediately rejected.

MATERIAL AND METHODS II

The deaths in the other sector of the province of Huesca were analysed, and certain difficulties were encountered in accessing the registry of their vaccinations in the HCE.

Subsequently, it was decided to change the methodology by undertaking a study of a nursing home in which the number of deaths was very high, in order to carry out a new study with a larger sample and concentrated data accessible from our intranet.

RESULTS II

The number of deaths due to COVID-19 in the Huesca Sector, with a similar population served, is 84 compared to 20 in the Barbastro Sector, more than four times higher.

Data is accessed from an old people's home that had 94 inmates on 08/11/2019, of which 25 have died from COVID-19, which reveals the finding that more people have died from COVID-19 in that old people's home with 94 inmates (25 deaths) than in our health sector with 111,490 (20 deaths), in a proportion 1000 times higher.

The lack of registration in EHR, due to a computer problem, was solved by gaining access to the manual register of Primary Care of vaccination in the residence, with the following results:

- Of the 80 people vaccinated with the adjuvant vaccine, 24, or 30%, have died.
- Of the 14 not vaccinated, 13 are still alive today, and one has died, 7% have died.
- No differences are observed in the age distribution of the dead and the survivors.
- Therefore, the death rate of those who have been vaccinated with the registered adjuvant vaccine quadruples that of the unvaccinated, for a sample already of 94 individuals. 4

CONCLUSIONS II

The analysis of the data from the residence studied allows two conclusions to be drawn:

1st Conclusion: the regime of internment in the nursing home, with the consequent higher risk of coronavirus infection, would not be directly associated with a higher risk of death from COVID-19 in those over 65 years of age,

as shown by the high survival rate of inmates who did not have the risk factor of having received the influenza vaccination (13 of 14).

2nd Conclusion: the greatest risk factor for death from COVID-19 in people over 65 years of age is again the fact of having received influenza vaccination with the adjuvant vaccine. This conclusion is consistent with that of the first part of the study.

A geographical-social-sanitary component is therefore observed that can be investigated in more depth, which leads to a search for a possible theoretical mechanism of action.

DISCUSSION

Two theoretical possible mechanisms of action are proposed for the increased risk of death from COVID-19 in people over 65 years of age vaccinated with the adjuvant flu vaccine in the 2019-2020 campaign:

Theoretical mechanism 1: Microbiological contamination of the vaccine itself

The Microbiology Service of our centre was asked to carry out a PCR test on the contents of a syringe left over from the campaign, from the batch of adjuvant vaccine administered to more deaths. The result of the test was negative. Therefore, a possible contamination of the vaccine itself with SARS-CoV-2 is ruled out, which is expected.

Theoretical mechanism 2: Causal agent included in the composition of the vaccine

The composition of the adjuvant vaccine administered to those over 65 years of age was studied as part of the Public Health campaign in the Community of Aragon, Chiromas®, whose technical data sheet (3) reports that it contains the same flu virus surface antigens as the Chiroflu® vaccine (4), which is the one that has been administered to us health workers, but differs in that Chiromas® also contains the adjuvant component MF59C.1, composed of 9.75 mg squalene; 1.175 mg POLYSORBATE 80; 1.175 mg sorbitol trioleate; 0.66 sodium citrate; 0.04 mg citric acid and water for injection.

Adjuvants are substances used in combination with a specific antigen that produce a more robust immune response than the antigen alone (5).

Squalene is a natural hydrophobic hydrocarbon originally obtained for commercial purposes from shark liver oil, but which is produced by all complex organisms, including humans, since it is a precursor of cholesterol. It is therefore not a foreign product to our body.

Of the remaining components of the adjuvant, an initial literature search was conducted which led to the study being focused on POLYSORBATE 80, a cosmetic ingredient also known as TWEEN-80 and other names, and with the initials E-433. In the INCI list (International Nomenclature of Cosmetic Ingredients) it is called POLYSORBATE - 80, as indicated in the technical information sheet of Acofarma (6).

Chemically, POLYSORBATE 80 has a hydrophilic part and a lipophilic part, which allows it to improve the solubility in water of hydrophobic molecules such as squalene, stabilizing the emulsions.

The effectiveness of POLYSORBATE 80 as a surfactant agent is confirmed by the importance of the medicines that include it to make possible the parenteral administration of macromolecules of the size and complexity of monoclonal antibodies (adalimumab, infliximab, tocilizumab, secukinumab...), vaccines, epoetin alpha, anakinra, amiodarone... in injectable solution, or triamcinolone acetonide in suspension.

POLYSORBATE 80 is very well tolerated and is not irritating to the skin and mucous membranes topically, but the same Acofarma technical information sheet (6) warns that "polysorbates have been associated with serious adverse effects, including death, in low birth weight infants who were administered parenteral preparations with polysorbates".

It has been described that POLYSORBATE 80 is not inert in the body, but is pharmacologically and biologically active (7).

The warnings regarding POLYSORBATE 80 are repeated in several technical data sheets, leaflets and prescription information of several drugs that include it:

- Amiodarone (Trangorex®): The data sheet warns that cases of hepatotoxicity have been reported with amiodarone after intravenous administration that could be due to the solvent (POLYSORBATE 80) that carries it, instead of the drug itself (8).
- Docetaxel (various drugs): The US package insert warns that infusional reactions to systemic chemotherapy with docetaxel have been attributed to the vehicle, POLYSORBATE 80 (9).
- Etoposide (Vepesid®): In animal models, POLYSORBATE 80 included as a vehicle of the intravenous formulation has been shown to induce histamine release and cause hypersensitivity reactions (10).

FINAL CONCLUSION I: HYPOTHESIS ON THE CAUSE OF COVID-19 IMMUNOLOGICAL

A hypothetical mechanism consisting of a possible immunological interference is proposed, which requires the concurrence of 3 elements:

- Relatively recent previous exposure of the subject to the administration of POLYSORBATE 80 by parenteral route, either through the adjuvant flu vaccine or other parenteral drugs containing it.
- Immunological status of the non-optimal subject: advanced age, concomitant autoimmune pathologies, immunosuppressive treatments...
- Subsequent infection with a strain of the SARS-CoV-2 coronavirus

That is, neither the polysorbate nor the coronavirus would be able to trigger the hypersensitivity reaction by themselves. The possible interference between acquired immunity against POLYSORBATE 80 and coronavirus infection would occur at the time of viral replication inside the infected cells, and in subjects with a not 100% efficient immune status.

FINAL CONCLUSION II: HYPOTHESIS ON THE EXISTENCE OF TWO TYPES OF CORONAVIRUS STRAINS ACCORDING TO THEIR IMMUNE BEHAVIOUR

Here we analyze a new variable: The contradictory results of PCR tests obtained for several patients in our center, with alternative results (+) and (-), seem to suggest the idea that at least two types of SARS-CoV-2 strains could coexist, one type would give a positive PCR and the other would give a negative one. During the replication process in the infected cell, a mutation from one type to another type of coronavirus strain could occur. This is a theoretical deduction based on the observation of the evolution of PCR tests of patients affected with COVID-19.

Certain strains of the coronavirus, when replicating in a cell of the pulmonary mucosa or the vascular epithelium, would cause it to express on its surface some antigen similar to polysorbate, and would be responsible for the immune interference, by confusing a not 100% efficient immune system, making it use the immunity acquired against polysorbate against the cells of the individual in which that strain is replicating, attacking and destroying them as foreign cells, triggering a severe hypersensitivity reaction, the inflammatory process known as "cytokine storm" (11), which is the one that would ultimately cause death. These strains could be called interfering strains.

We know that the clinical complications of this hypersensitivity reaction can manifest themselves as an acute respiratory distress syndrome (ARDS), disseminated vascular coagulation, acute pancreatitis (12)..., depending on the cells in which the coronaviruses are replicating, which are attacked by the patient's autoimmune reaction, with the very serious known consequences.

Other strains, on the contrary, would not have this antigenic effect, and would not produce immune interference, and we could call them non-interfering strains. This would explain the fact that there are certain individuals with a not 100% efficient immune system and to whom in November-December 2019 POLYSORBATE 80 was administered parenterally as part of the adjuvant vaccine, who only suffer the initial mild infectious syndrome due to SARS-CoV-2, and not the severe immune syndrome. These individuals would normally generate antibodies against those non-interfering coronavirus strains.

But in these latter individuals, it could be the case that before the definitive elimination of all the coronaviruses, in a process of replication, an interfering strain would emerge by mutation, giving rise to the described immune interference, and a "late cytokine storm".

There is no literature that supports any of these hypotheses, since they are theoretical approaches based on our observation during healthcare practice.

FINAL CONCLUSION III: HYPOTHESES ON THEORETICAL POSSIBLE TREATMENTS IN CASE THE CAUSE OF THE IMMUNOLOGICAL COVID-19 WAS THE IMMUNOLOGICAL INTERFERENCE WITH THE POLYSORBATE-80

As a logical consequence of the above conclusion, if the investigation has taken us so far, why stop? Given that the focus of the study is fundamentally pharmaceutical and theoretical, we are presented with the opportunity to address, now, the treatment of the immunological phase of COVID-19 in case the hypothesis of immunological interference should prove to be true.

If the hypothetical immunological interference posed theoretically was mediated by anti-POLYSORBATE-80 antibodies that were being "mistakenly" used against the own cells in which the coronavirus was replicating in the severe immunological phase of COVID-19, a theoretical way at least "daring" to redirect those antibodies would be to put within reach their true objective: the POLYSORBATE-80. How? by administering it at that time by parenteral route, for example, by re-administrating the adjuvant flu vaccine.

For this measure there is no bibliography either, since it is merely a theoretical approach.

However, for other treatments the literature is extensive and contradictory, and so we focus on the results of care in our center, and the subjective perception that two drugs could have been effective: tocilizumab and anakinra.

The two drugs have already been mentioned in this article because their composition contains POLYSORBATE-80, which leads us to the theoretical approach of the last hypothesis of this work: "Could the POLYSORBATE-80 contained in these drugs as an excipient be the real pharmacologically active agent against the "cytokine storm", by redirecting the antibodies-ANTIPOLYSORBATE-80 to act against it, freeing the patient's cells from the massive attack of these antibodies, and thus slowing down the autoimmune process? ".

Nor is there any literature for this last point, again merely theoretical.

FINAL CONCLUSION IV: GEOGRAPHICAL EXPLANATION

From another point of view totally different from the previous ones, the hypothesis would theoretically explain facts observed in the pandemic, such as the following:

- Geographical differences in COVID-19 cases worldwide, focusing initially on the northern hemisphere (Europe, United States, Mexico...), where pre-winter flu vaccination was carried out, while in the southern hemisphere it was autumn (13).
- Late appearance of COVID-19 in Brazil, where the influenza vaccination campaign began on 23 March 2020 (14), followed by an exponential increase in the number of people affected (15).
- Geographical differences in COVID-19 cases at the European level, where there are very low rates of influenza vaccination in people over 65 in Eastern European countries such as Estonia, which is less than 5%, compared to Spain, the United Kingdom, France or Italy, with rates of 50-60% (16). There are also differences in access to vaccines and the type of vaccines used. For example, in Estonia, the flu vaccine is paid for (17).

Geographical and social differences at national level, with higher rates in residential and rural elderly areas, where the vaccination rate is higher than in residents in their own homes and in urban areas. Aragón is an emblematic case of rural and residential care, with a higher rate than that of its low population density (18), (19).

FINAL SUMMARY

This theoretical study provides:

1. A theoretical possible immunological mechanism to explain that patients who fall ill with COVID-19 and have the adjuvant flu vaccine in place die more than patients with COVID-19 who have not been vaccinated for influenza in the last campaign, focusing on an excipient for which there are described adverse immunological reactions.
2. A theoretical explanation for the contradictory results of PCR tests obtained throughout the evolution of COVID patients.
3. A theoretical explanation for the positive results obtained with parenteral drugs containing POLYSORBATE-80 (tocilizumab and anakinra).
4. A theoretical explanation for the geographical differences observed in the distribution maps of the pandemic.

Influenza vaccination is never questioned, since a quadrivalent flu vaccine without POLYSORBATE-80 is available as an alternative for active immunisation of adults, including pregnant women, and children from 6 months of age and older. This vaccine is also the first to appear in the composition recommendation by the WHO, according to the SEMERGEN Discussion Paper on Quadrivalent Vaccine (20).

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